PERINATAL COMPLICATIONS IN CHILDREN, WHICH WERE BORN AFTER ASSISTED REPRODUCTIVE TECHNOLOGIES WITH IN VITRO FERTIZILATION

Abdujapparova Naziraxon Erikli qizi
Obstetrician-gynaecologist at
Republican Specialized Scientific and Practical Medical
Center for Mother and Child Health of Fergana Branch
https://doi.org/10.5281/zenodo.13879640

Introduction. In fertility problems affect 8-12% of couples of reproductive age. Singletons born after IVF have a higher risk of adverse perinatal outcomes such as gestational age and low birth weight, as well as multiple meta-indicators of preterm birth (PTB), low birth weight and small for gestational age (SGA). - confirmed by analyses. The relative risk (RR) after IVF for PTB is 1.54 and 1.84 compared with natural singletons and the odds ratio (OR) was 1.55. The development of IVF techniques over time and antagonist or low-dose gonadotropin protocols and the assessment of perinatal outcomes of recent cohorts remain important. Many factors associated with IVF may be associated with negative perinatal outcomes. Gonadotropin stimulation increases the risk of LBV or SGA at birth, particularly when supraphysiological estradiol concentrations are reached on the trigger day or when many oocytes are collected. Gonadotropin stimulation is also associated with a higher risk of ovarian hyperstimulation syndrome, pregnancy-associated hypertension, and gestational diabetes for the mother, and appears to be independently associated with preterm birth. Otherwise, singletons resulting from moulting cycles pose significantly lower risks for PTB and LBV, but higher risks for gestational age and higher birth weight. By delaying embryo transfer in moulting cycles, gonadotropins have no direct effect on pregnancy. Epigenetic changes are triggered and DNA methylation is influenced by embryo cultures, cryopreservation and laboratory methods . In addition, parental age, health and subfertility are associated with higher perinatal risk. PTB is supported by a meta-analysis. In studies with indifferent pregnant siblings, differences in consanguinity were less pronounced or non-existent, leading to the conclusion that primary infertility also plays a role. The Bern IVF cohort was established to evaluate obstetric, perinatal and long-term outcomes in children born after different IVF procedures stimulated and unstimulated performed in a single center with standardized laboratory and embryo culture conditions. Natural cycle IVF (NC-IVF) is based on the concept of natural follicle recruitment and

single oocyte selection, while the growth of multifollicular oocytes is common in gonadotropin-stimulated IVF. NC-IVF can serve as a model for the development of natural ovulation, and comparison with SIVF allows assessing the impact of gonadotropin stimulation on perinatal outcome. The aim of this study was to first compare the perinatal outcomes of the Bern IVF cohort with those of a fertility cohort at a third centre and the All Live Birth Registry; and second, the registry to determine the effect of Gonadotrophin stimulation by comparing and NC-IVF for children born in Switzerland.

Materials and methods. The Bern IVF cohort includes couples treated at the Department of Gynecological Endocrinology and Reproductive Medicine. Data were collected at the Clinical Trials Unit of the University of Bern using the electronic study data capture tools. Redcap is a secure web-based platform designed to support data collection for research. All women born between November 2010 and August 2018 were included, regardless of any health status. Women with missing information on gestational age and birth weight were excluded in case of multiple births and perinatal death.

A cohort of women from the ODS Department of Obstetrics and Gynecology at the University Hospital of Bern were followed up during regular ultrasound visits during the first trimester and until delivery. In this study, data on conception, pregnancy and delivery were collected and singleton women with a live birth were included in the analysis. All women without pre-existing chronic diseases or disorders were included. Only women treated with IVF, ovarian stimulation or fertilization, low perinatal mortality, women refusing further use of their medical data for the study and excluded cases with missing information on gestational age or birth “n” analysis.

The Swiss Live Birth Registry of the Federal Statistical Office collects systematic data on all live births in Switzerland. Only basic data on mothers age, ethnicity, occupation, gender and infants gestational age, birth weight, length, sex, siblings were collected; no medical data on the health of the mother, the newborn, or information on the conception, pregnancy and birth process were included. All live births registered between November 2010 and August 2018 were included (n = 669,390). Births with missing valid identifiers (N = 6,942), multiple pregnancies (N =24,472), gestational age below 22 weeks or 500 g (N = 541) below birthgility, maternal age above 45 years at birth (N = 960) and gestational age and birthgilith (N = 2,479) were excluded from the analysis. A gestational age of 22 weeks is the difference between abortion and stillbirth according to Swiss law. They were monitored by ultrasound and measurement

of estradiol and luteinizing hormone (LH). When the follicle diameter reached at least 16 mm and estradiol was 700 pmol/L, women received a trigger shot of 5000 IU human chorionic gonadotropin (hCG) to induce ovulation. Oocyte loading took place over 36 h without subsequent anesthesia. Clomiphene citrate 25 mg to reduce the risk of premature ovulation starting on day 7 of the cycle or ibuprofen 400 mg three times daily taken by the woman 48 hour before oocyte retrieval. For research, 75 to 350 IU of gonadotropin per day were administered , and an antagonist or agonist protocol was performed. In SIVF treatment, stimulation was monitored by ultrasound and measurement of serum estradiol concentration. When more than two leading follicles reached a diameter of at least 18 mm with appropriate estradiol concentration, ovulation was induced by injection of CG by females. Oocytes were retrieved 36 h later under sedation.

Oocytes were fertilized by standard intracytoplasmic sperm injection (ICSI) or in vitro. Standard embryo culture conditions were consistent across both groups. New embryos were ultrasound-guided in the cleavage phase for 2 or 3 days in culture. Women maintained the luteal phase by administering 200 mg micronized progesterone twice daily as needed. Switzerland did not allow longer embryo cultures until 2017 and excess zygotes were vitrified. All three datasets provided information on the primary outcomes, birth weight and gestational age. The percentage of birth weight was calculated for each singleton live birth according to the formula provided. Data on the duration of labour were available in the Bern IVF cohort and SLBR. The mode of delivery was compared between the Bern IVF cohort and ODS. A caesarean section was defined as secondary if labour had already started contractions, bleeding or rupture of membranes. The reasons for caesarean section were divided into maternal, fetal or emergency. Women with regular menstrual cycles 26-32 days can choose the treatment at their own discretion, since NC-IVF requires a regular cycle. Information on maternal age, parity and fetal sex at delivery was available in all datasets. Additional information on smoking and maternal body mass index from the Bern IVF and ODS cohort during pregnancy was used. **Results**. First, primary perinatal outcomes were compared, and second, delivery procedures and reasons for caesarean section were described. To compare the three data sets, adjustments were made for maternal age, parity and sex of the child. To compare the Berne IVF cohort and ODS, maternal BMI and smoking during pregnancy were additionally adjusted. Continuous outcomes such as fertility, gestational age, survival and live birth rate were

assessed using univariate and multivariate linear regression. To report RR and 2500% CI, modified Poisson regression was used for associations with binary endings such as LBT (<10 y), PTB (<2004 weeks of gestation), SGA (<10th percentile), and cesarean section. Maternal identifiers were used as cluster variance estimates to account for singletons born to the same mother. To assess the effect of gonadotropin stimulation, singletons born after were compared with those born after NC-IVF, but both subgroups were compared with SLBR. The proportion of missing data was very low: two participants in the Bern IVF cohort were lost to follow-up (<0.01%); 18 (<0.1%) in the ODS and 2479 (<0.005%) in the SLBR were excluded because of missing birth or pregnancy data. The interpretation of birth weight as an outcome has been controversial because it is closely related to gestational age. Perinatal epidemiologists recommend not adjusting birth weight for gestational age but estimating birth weight of singletons, which is done for sensitivity analyses 37 weeks of gestation. A p value of <0.05 is considered statistically significant.

The analysis included 636,639 deliveries. It shows the exclusions and final study populations: the Bern IVF cohort (N =311), third-center ODS (N =2332), and SLBR (N =633,996). Mothers in the Bern IVF cohort were on average 3.6 years older and more often primiparous than non-IVF mothers (95% CI 3.2 to 4.1 years); and compared with ODS, they smoked less and had a lower BMI.

Mean gestational age was comparable in the Berne IVF cohort and SLBR singletons but lower in ODS singletons P < 0.001) . Singletons and SLBRs in the Berne IVF cohort had comparable risks for PTB, which were higher for ODS singletons (P = 0.03). Adjusted mean birth weight was lower in the Berne IVF cohort than in SLBRs, but this difference disappeared when the comparison was restricted to children born after the period or adjustment. All model covariates were strong.

Birth weight percentage: the mean live birth rates did not differ but were below 50th percentile for the three cohorts. The Berne IVF cohort and singleton ODS had an increased risk of SGA birth compared with SLBR. Whereas for children born at term, the risk of SGA was not statistically different for singleton ODS (RR 1.07, 95% CI 0.95 to 1.20; P = 0.24) and singleton IVF (RR 1.27, 95% CI 0.96 to 1.70; P = 0.10), compared with both SLBR.

Discussion. Compared with singletons in the Berne IVF cohort showed no difference in gestational age and fertility rates, and no increased risk for LB or PTB. On the other hand, they showed lower mean birth weight and higher risk of SGA. There were no differences in the Berne IVF cohort compared with ODS. IVF

mothers were older and often primiparous. Singletons born after SIVF were lower than average birthletons and had a risk of becoming SGA compared with it, while singletons born after SIVF were similar to SLBR singletons due to increased pressure. The strengths of this study are the detailed and comprehensive information collected in the Bern IVF cohort on conception, infertility treatment, pregnancy course and perinatal outcomes. The study included the use of the population-based SLBR as a comparison group and it contributes to the limited literature on perinatal outcomes in children born after NC-IVF.The sample size of the Bern IVF cohort is limited, so for all comparisons the focus is on reporting the 95% CI. The characteristics of women choosing NC-IVF and those choosing SIVF may be different. In Switzerland, IVF treatment is not subsidized; this hinders randomized controlled trials. The ODS data are collected at a third center, which is a neonatology department where patients are referred for treatment of pregnancy complications or for a second opinion. The ODS mainly consists of high-risk groups; selection bias is an issue. SLBR includes all children born alive, regardless of how long they survive after birth, and thus perinatal deaths occurring within the first week of life. The SLBR data include births in the Bern IVF cohort and a portion of births in the ODS. Detection of duplicate deliveries was not dependent on the anonymized SLBR data in the cohorts. SLBR also includes pregnant women who became pregnant after fertility treatment in Switzerland or abroad. However, compared to SLBR, the proportion of both cohorts is too small to influence the average outcome figures.Different demographic characteristics of parents undergoing IVF higher age, lower parity have been demonstrated in other countries; these characteristics may reflect a transition to higher childbearing age and a delay in diagnosis of parental infertility. On the other hand, IVF mothers in this study had fewer pregnancy complications and a healthier lifestyle compared to ODS mothers; this may positively impact perinatal outcomes. Regarding perinatal outcomes, the results of the current study are encouraging; the results of the previous meta-analysis were not confirmed. In this study, gestational age and fertility rate were not lower and the risk of PTB and LBV was not increased after IVF. And the low crude mean live birth rate and the risk of SGA in IVF infants could only be confirmed in a flawed analysis. Both PTB and intrauterine growth restriction reduce birth weight, and SGA is a result of intrauterine growth restriction, which sometimes requires induction of labor or cesarean section. Also in this study, cesarean section was associated with LBV and PTB. Maternal age and parity are other independent risk factors associated with perinatal

outcome. The current results are partly explained by the high age and low parity of IVF mothers. IVF may affect intrauterine growth, but maternal factors seemed more important in this study. Endometrial receptivity or there are other possible explanations for vanishing twins that cannot be controlled.

A separate study in Switzerland found that regional differences mainly influenced birth weight; maternal age influenced gestational age, but surprisingly, regional differences in caesarean section rates were not associated with differences in fertility or gestational age. Fertility rates below 50 were observed for all three populations. The current fertility rates are based on children born in England and are not sex-specific. They were not fully converted to Swiss singletons. The low birth weight percentage of Swiss cohorts may reflect different distributions of parental traits. Fertility rates specifically designed for US singletons showed very little difference population standards. Similar average fertility rates are encouraging for this IVF population. Three cohort studies have assessed the effects of gonadotrophin stimulation compared with NC-IVF. In the Japanese IVF registry study, data from 8,224 singletons after NSIVF were compared with data from 610 after NC-IVF. For agonist and antagonist protocols, the odds ratio was 1.60–1.72. The UK IVF registry study found data from 98,667 stimulated and 262 stimulated new cycles and showed a trend towards higher contrast only for LBT (AOR 1.58, 95% CI 0.96 to 2.58) and PTB (AOR 1.43, 95% CI 0.91 to 2.26). In a small US study of 174 stimulated and 190 unstimulated IVF cycles, birth weight decreased by 163 g; the proportion of LBV infants was 1.0% in NC-IVF and 8.6% in sivf. This may be explained by a significantly higher proportion of very preterm births (<0.5 weeks gestation) in the sivf group (32% vs 6.3%). Increased pressure-present on IVF analysis showed a risk for PTB (RR 1.32, 95% CI 1.05 to 1.66) but not for LBV (RR 2.98, 95% CI 0.54 to 16.29) followed by stimulated IVF. The reduced risk of PTB and LBV after frozen embryo transfer may be due not only to cryopreservation but also to the absence of gonadotropin use in the pre-transfer cycle. New studies comparing NC-IVF with natural shedding cycles may shed more light on the specific impact of cryopreservation on perinatal outcomes. The current study did not find a lower mean birth weight, decreased gestational age, or higher risk of PTB and LBV in sivf compared with NC-IVF. However, sivf births were found to have a higher risk of low birth weight and SGA compared with slbr, while perinatal outcomes of NC-IVF were similar to those of SLBR. After adjustment, the risk of LBV remained high, but the risk of SGA was attenuated. It can be concluded that SIVF is

associated with a slightly higher risk; maternal age and parity may partially explain this. However, the risk difference in this study is much lower than in other studies. Gonadotropin dose and individual ovarian response depend on birth weight and SGA. Both superovulation and supraphysiological estradiol concentrations are associated with adverse outcomes as they disproportionately affect the endometrium, implantation, placentation and intrauterine growth. An effect on endometrial gene expression has been demonstrated in endometrial biopsy tissue analysis from SIVF and NC-IVF women, which is critical for tissue remodeling and implantation. Another explanation may be the healthy lifestyle of mothers in the Bern IVF cohort. Several studies have reported higher rates of cesarean section or assisted vaginal delivery in IVF infants. Although there are no high risk factors for operative and assisted vaginal delivery in IVF pregnancies and preterm labor, shorter labor duration was reported by an Italian study. The highest rates of cesarean section in singletons undergoing IVF were reported by the Australian Newborn Registry Study. Conception by IVF appeared to influence the gynecologist's and parents' decisions regarding pregnancy monitoring, diagnostic interventions, and delivery mode. Pregnancies after IVF are often closely monitored and undergo more diagnostic interventions; this may result in primary cesarean section. This phenomenon has been called the "precious baby effect". In an American study, pregnancy complications and higher maternal age were the main reasons for the increased cesarean section rate after IVF. Women with subfertility also had a higher cesarean section rate than fertile women. Maternal age, subfertility and comorbidities may be related to other treatments or the "precious baby effect". In the current study, the high cesarean section rate in IVF was not observed after adjusting for maternal age, parity and sex of the child. These findings may reflect different characteristics of IVF mothers: this is not surprising, since women with ODS have a higher rate of pregnancy complications and represent a high-risk group. However, the high rate of primary cesarean section in IVF women may be an indication to avoid risk during delivery. The caesarean section rates in the ODS and Bern IVF cohort are higher than the 32% caesarean section rates in Switzerland Federal Statistical Office. It is important to note that caesarean section rates are also strongly influenced by cultural concepts and regional differences such as urbanization. It is therefore difficult to conclude whether pregnancy and birth are subject to the necessary medical interventions or whether obstetricians and parents are especially careful in cases where pregnancy is difficult to achieve.

However, in primiparous women, the mode of delivery influences the mode of delivery in subsequent pregnancies, and caesarean section also influences the success of subsequent ART treatment, so it is particularly important to avoid unnecessary caesarean sections in low-risk primiparous IVF pregnancies. Further research into cesarean section in IVF pregnancies or after a long period before conception will help to understand the underlying factors.

Overall, the children in the Bern IVF cohort did not show perinatal outcomes due to infertility treatment. However, gonadotropin stimulation may have additional effects on intrauterine growth and birth weight. The risk of low birth weight and SGA was increased after stimulated IVF in the unadjusted analysis and the risk of low birth weight in the adjusted analysis compared with SLBR. An analysis including national data on all IVF children will be important to verify these findings.

References:

1. Al-Inani, HG, Yousef, MA, Ayeleke, RO, Brown, J, Lam, Vt, Broekmans, FJ Gonadotrophin-hormone antagonists for assisted reproductive technologies. The Cochrane Core System. Wow. 2016; 2016cd001750. doi: 10.1002/14651858. CD001750.
2. Natural cycle FET was programmed versus frozen embryo transfer (FET) pregnancies after 1,136 singleton pregnancies Asser RL, Spangmose AL, Aaris Henningsen AK, Clausen TG, Ziebe S, Jensen RB, Pinborg A. Negative obstetric and perinatal outcomes. Fert. Sterile. 2021; 115: 947–956. doi: 10.1016/j.fernstert.2020.10.039
3. Health effects of smoking during pregnancy and the postpartum period: an umbrella review. BMC pregnancy childbirth 2021;21:254. doi: 10.1186/s12884-021-03729-1
4. Berntsen S.V., Wennerholm, W.-B., Laivuori, H., Loft, A., Oldereyd, H. B., Bente Romundstad, L., Berg, K., Pinborg, A. Children's health conceived by art: the chicken or the egg? Hum. Rep. Update 2019; 25: 137-158. doi: 10.1093
5. Bonagura, T. V., Pepe, G. J., Enders, A. C., Albrecht, E. D. Early pregnancy in the baboon suppresses ectopic trophoblastic vascular endothelial growth factor expression by estrogens and in habits uterine spiral arteries. Endocrinology 2008; 149: 5078-5087. doi: 10.1210/en.2008-0116
6. Conforti, A., Picarelli, S., Carbone, L., La Marca, A., Venturella, R., Vaiarelli, A., Cimadomo, D., Zullo, F., Rienzi, L., Ubaldi, F. M., Alviggi, C. Perinatal and singleton pregnancy obstetric outcomes compared with cryopreserved blastocyst follow-up: a meta-analysis. Reprod. Biomed. Online 2021; 42: 401–412. doi: 10.1016/j.rbmo.2020.09.029

7. Devroy, P., Bourgain, C., McClone, N. S., Fauser, B. C. J. M. Reproductive biology and IVF: ovarian stimulation and endometrial receptivity. Endocrine Trends Metab. 2004; 15: 84–90. doi: 10.1016/j. tem.2004.01.009
8. Dickey, R. P., Xiong, X., Prigian, G., Klembel, M. C. In vitro fertilization with gestational age below Singleton birthgility in the United States. I am. J. Obstet. Gynecol. 2016; 214. doi: 10.1016/ajog.2015.08.008
9. Goizis, A., Håberg, S. E., Hanevik, H. I., Magnus, M. C., Kravdal, O. (2015). Demographics of reproductive technology fertility in a Nordic country. Hum. Rep. 2020; 35: 1441–1450. doi: 10.1093/humrep/deaa055
10. Goizis, A., Remes, H., Martikainen, P., Klemetti, R., Myrskyl, M. Health care reproductive and fertility outcomes: a within-family analysis using Finnish population registers. Lancet 2019; 393: 1225-1232. doi: 10.1016/S0140-6736(18)31863-4
11. Effect of nicotine and maternal BMI on fetal birth weight. BMC pregnancy childbirth 2021;21:127. doi: 10.1186/s12884-021-03593-z
12. Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neill, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., Duda, S. N. The Redcap consortium: building an international community of software platform partners. J. Biomed. Aware. 2019;95103208. doi: 10.1016/jbi.2019.103208
13. Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J. G. Research Electronic Data Capture (Redcap)—a metadata methodology to support translational research informatics and the business development process. J. Biomed. Aware. 2009; 42: 377–381. doi: 10.1016/J. JBI.2008.08.010
14. Henningsen, A. A., Gissler, M., Skjaerven, R., Berg, K., Tiitinen, A., Romundstad, L. B., Wennerholm, W. B., Lidegaard, O., Andersen, A. N., Forman, J. L., Pinborg, A. (2015) Perinatal health trends after reproduction: the Scandinavian CoNARTaS Group study. Hum. Rep. 2015; 30: 710–716. doi: 10.1093/humrep/deu345
15. Henningsen, A. KA, Pinborg, A. Birth and perinatal outcomes and complications for neonates in the lower sect. Semin. Neonatal Fetal Medicine. 2014; 19: 234–238. doi: 10.1016/j. sin.2014.04.001
16. Henningsen, A. K. A., Pinborg, A. A., Lidegaard, Westergaard, K., Forman, J. L., Andersen, A. N. Assisted reproductive technology and the concept of spontaneity in singleton brothers born after perinatal outcome: the Danish National Sibling Cohort Study. Fert. Sterile. 2011; 95: 959–963. doi: 10.1016/j.fernstert.2010.07.1075

17. Kamath, M. S., Kirubakaran, R., Mascarenha, M., Sunkara, S. K. Perinatal outcomes and natural cycle of IVF after stimulation: a systematic review and meta-analysis. Rep. Biomed. Online 2018; 36: 94-101. doi: 10.1016/j.rbmo.2017.09.009
18. Hashan, A. S., Kenny, L. C. Effect of maternal body mass index on pregnancy outcome. Eur J Epidemiol. 2009; 24: 697–705. doi: 10.1007/s10654-009-9375-2
19. Kohl Schwarz, A. S., Burkard, S., Mitter, W. R., Leichtle, A. B., Fink, A., Von Wolf, M. Short-term use of ibuprofen before ovulation. Facts Vis Visions. ObGyn. 2020b; 12: 179-184
20. Kohl Schwarz, A. S., Calzaferri, I., Roumet, M., Limacher, A., Fink, A., Vuest, A., Weidlinger, S., Mitter, B. R., Leeners, B., Von Wolf, M. Follicular flushing results in higher oocyte yield in monofollicular IVF: a randomized controlled trial. Hum. Rep. 2020a; 35: 2253-2261. doi: 10.1093
21. Kohl Schwarz, A. S., Mitter, W. R., Amilidi-Mohr, S., Fasel, P., Minger, M. A., Limoni, S., Zwahlen, M., Von Wolf, M. Young gestational age infants undergoing gonadotropin-stimulated in vitro fertilization have supraphysiological ovulation in response to estradiol levels. Acta Obstet. Gynecol. Scand. 2019; 98: 1575–1584. doi: 10.1111/aogs.13691
22. Kolibianakis, EM, Collins, J, Tarlatzis, BC, Devroy, P, Diedrich, K, Griesinger, G. Among patients treated for IVF with gonadotrophin-GnRH analogs, does the probability of live birth depend on the type of analog used? A systems review and meta-analysis. Hum. Rep. Update 2006; 12: 651-671. doi: 10.1093/humupp/dml038